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Duregon, Eleonora; Volante, Marco; Guzzetti, Stefano; Rapa, Ida; Vatrano, Simona; Papotti, Mauro. Images in Endocrine Pathology: Unique Composite Adrenal Adenomatoid Tumor, Ganglioneuroma, Myelolipoma, and Cortical Nodular Hyperplasia. ENDOCRINE PATHOLOGY. None pp: 1-4. DOI: 10.1007/s12022-017-9480-9

IMAGES IN ENDOCRINE PATHOLOGY: UNIQUE COMPOSITE ADRENAL ADENOMATOID TUMOR, GANGLIONEUROMA, MYELOLIPOMA AND CORTICAL NODULAR HYPERPLASIA

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Source of support: Supported by a grant from AIRC, Milan, (no. IG/14820/2013 to MP).

Conflict of interests: The authors declare that they have no conflict of interests.

CASE HISTORY

A 48-year-old male patient had a surgical resection of a right testis seminoma. During preoperative imaging studies, a solitary nodule of the left adrenal gland was found. Since the suspected pre-operative diagnosis was a nonfunctioning cortical adenoma, in the absence of hormonal hyper-incretion effects, the adrenal lesion was removed six months after the testis surgery.

WHAT IS YOUR DIAGNOSIS?

Histopathologic diagnosis: Composite Adrenal Adenomatoid Tumor, Ganglioneuroma, Myelolipoma and Cortical Nodular Hyperplasia

The adrenalectomy specimen consisted of a bilobated tumour measuring 4 cm in its maximum diameter with a pale grey and partly yellowish, smooth cut surface. There were a few cystic spaces of 0.5 to 1 cm, but neither hemorrhage nor necrosis were noted. A rim of cortical tissue at the periphery was found. Microscopically, four different morphological patterns were found (**Figure 1**). The first was a well circumscribed area, composed of interweaving fascicles of Schwann cells, with no immature element, in a myxoid stroma containing mature ganglion cells and scant adipose tissue (**Figure 2A, B**). The other three components were intermingled one into each other, and distinct from the former. Among them, anastomosing tubules and cleft-like spaces of variable size and shape were observed, some of which arranged in multiple microcysts and separated by fibrous stromal bundles. These structures were lined by plump epithelioid or flattened cells resembling endothelial cells (**Figure 3A, B**). such cells merged in some areas with nests of cells having a prominent vacuolization and eccentrically placed nuclei conferring a signet ring cell appearance. The nuclei were otherwise uniform and round to oval, with no pleomorphism nor significant mitotic activity. In addition, there were scant islands of adipose and hematopoietic

tissues resembling mature bone marrow (**Figure 1B**), with megakaryocytes, erythroid, myeloid and lymphoid cells, with no precursor myeloblasts. The third component, accounting for 40% of the whole lesion, was composed by hyperplastic adrenocortical tissue lacking evident fibrous capsule (**Figure 1C**). By immunohistochemistry, a peripheral neural sheat derivation was confirmed for the first lesion, being Melan A and Steroidogenic Factor 1 negative (**Figure 2C**) and S100 protein positive only (**Figure 2D**). Conversely, the microcystic and tubular structures covered by flattened cells displayed evidence of mesothelial differentiation, with a strong positivity for cytokeratin AE1/AE3, calretinin and WT1 (**Figure 3C**), in the absence of adrenocortical (Melan A, Steroidogenic Factor 1) and endothelial marker expression (CD31, CD34, ERG) (**Figure 3D**). Therefore, the morphological and immunophenotypical features of these lesions led to a diagnosis of a combined ganglioneuroma and adenomatoid tumor with foci of myelolipoma in an adrenal gland with nodular cortical hyperplasia.

COMMENT

To the best of our knowledge, both adenomatoid tumors and ganglioneuromas have been reported in association either with myelolipoma (1) (2) or adrenocortical adenoma (3) (4) or nodular cortical hyperplasia (5), but a quadruple combination of ganglioneuroma, adenomatoid tumor, myelolipoma and nodular hyperplasia in a single tumor of the adrenal gland has not been described in the literature, so far. The uniqueness of this case is emphasized by the fact that at least two of the tumor components (adenomatoid tumor and myelolipoma) arise from tissues that are presumably foreign to those of the adrenal gland. Adenomatoid tumors are benign neoplasms with mesothelial differentiation, which are usually found in the genital tract of both males (epididymis, testicular tunica, and spermatic cord) and females (uterus, fallopian tubes, and more rarely, ovary) (6). As the coelomic epithelium gives rise to both mesothelial lining and adrenal

cortex, it can be easily understood why adrenal glands may host mesothelial-derived neoplasms such as adenomatoid tumors, generally thought to derive from mesothelial inclusions. In addition, the close embryologic relationship between adrenal gland and the mullerian tract can explain both heterotopic adrenal cortical tissue in the periovarian region and adenomatoid tumor in the adrenal gland (7). Among various hypotheses underlying the development of myelolipoma (bone marrow embolization, embryonic primitive mesenchymal cells, dysregulation of hematopoietic cell apoptosis), the most consistent is the differentiation of undifferentiated mesenchymal cells to myeloid and lipoid tissues activated by systemic stress from chronic illness, necrotic tissue or high-energy trauma (8). Similarly to adenomatoid tumors, the presence of haematopoietic tissue in the adrenal gland can be explained embryonically because the adrenal cortex and bone marrow originate from the same mesenchymal tissues (9). This theory is supported by animal studies where myelolipomatous changes were seen after injecting necrotic tissues in rats (10). However, the relationship and pathogenetic links between the medulla and cortex and their tumors, and therefore whether both components grow independently or in an interrelated manner remains unresolved. The imaging characteristics of both adrenal ganglioneuroma and adenomatoid tumor are quite variable being some very similar to other adrenal tumors such as adrenocortical carcinoma and pheochromocytoma (11). Therefore, a definitive diagnosis can be obtained after surgery, only. In our case, the ganglioneuroma was a discrete tumor, while the adenomatoid tumor was intermingled with hyperplastic adrenocortical cells growing in a nodular fashion. Among the lesions encountered in this exceptional case, the most challenging for the pathologist is the adenomatoid tumor, as its lymphangiomatoid and microcystic-cavernous growth patterns could be interpreted as a vascular neoplasm, particularly a lymphangioma (12). However, the positivity for epithelial and mesothelial markers and the absence of vascular and lymphatic markers generally easily address to the correct differential diagnosis. In addition, the complex

tubules with adenoid appearance and those with a packed-solid growth with vacuolated cells may simulate metastatic adenocarcinoma or signet ring cell carcinoma, but the lack of pleomorphism, mitotic figures, necrosis, and cellular atypia rules out the suspicion of malignancy (13).

In conclusion, we reported an exceptionally rare benign adrenal lesion made of four components of different embryological derivation, which expands the potential repertoire of combined tumors occurring in the adrenal gland.

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FIGURE LEGENDS.

Figure 1. Representative areas of the four different morphological aspects found in the adrenal node: fascicles of spindle cells with minimal adipose tissue (**A**) and a rim of normal adrenal gland (top right); anastomosing tubules and multiple microcysts and separated by solid fibrous stroma (left) and islands of adipose and hematopoietic tissues resembling mature bone marrow (right) (**B**); hyperplastic adrenocortical tissue lacking evident fibrous capsule (**C**). (A-C: Hematoxylin & Eosin, original magnification 40X).

Figure 2. Interweaving fascicles of Schwann cells, with no immature element, containing adipose tissue (A) and mature ganglion cells (B). Ganglion cells (*left*) were negative for Melan A (**Figure 2C**) and positive for S100 protein (**Figure 2D**) (A, B: Hematoxylin & Eosin, original magnification 200X; C, D: immunoperoxidase, original magnification 400X).

Figure 3. Multiple microcysts and (A) with tubules and cleft-like spaces of variable size and shape (B). The structures are lined by plump epithelioid to flattened cells, occasionally having a prominent vacuolization conferring a signet ring cell appearance. These cells are positive for calretinin (C), but negative CD31 (D) (A-B: Hematoxylin & Eosin, original magnification 200X; C-D: immunoperoxidase, original magnification 400X).